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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/471,825	12/23/1999	SHUN Y. LIN	2092/OG278	7998

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EXAMINER
WELLS, LAUREN Q

ART UNIT	PAPER NUMBER
1617	

DATE MAILED: 07/02/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application N .	Applicant(s)	
	09/471,825	LIN ET AL.	
	Examin r	Art Unit	
	Lauren Q Wells	1617	

-- The MAILING DATE of this c mmunication appears on the cover sheet with the corresp ndenc address --

Period f r Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 April 2003 and 27 May 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-50 and 52-55* is/are pending in the application.

4a) Of the above claim(s) *3-5,11,30-32,39,48,54 and 55* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,6-10,12-29,33-38,40-47,49,50,52 and 53* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *26* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claims 1-50, 52-55 are pending. Claims 3-5, 11, 30-32, 39, 48 and 54-55 are withdrawn from consideration, as they are directed toward non-elected subject matter. The Amendment filed 5/27/03, Paper No. 25, amended claims 1-5, 9-10, 27-29, 35, 37, 38, and cancelled claims 51 and 56-67.

Applicant's arguments filed 4/7/03, Paper No. 23, are persuasive to overcome the 35 USC 112 rejection in the previous Office Action.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-2, 6, 7-10, 13-27, 29, 37-38, 41-43, 45-47, 49-50, 52-53, are rejected under 35 U.S.C. 103(a) as being unpatentable over Saslawski et al. (WO 99/33448).

The instant invention is directed to a composition comprising a sustained release layer and a fast release layer, wherein the sustained release layer comprising a water-soluble polymer and an active agent, and the fast release layer comprises a matrix forming agent and an active agent, wherein the composition is freeze-dried and lyophilized.

Saslawski et al. teach a tablet for the instant and prolonged release of one or more active substances. Exemplified is a tablet, wherein the immediate release granule comprises 94.12% EMP (active agent), 2.94%polyvinylpyrrolidone 30, 2.94% cross-linked carboxymethylcellulose (matrix forming agent), and the prolonged release granule comprises 71.7% EMP, 17.2% lactose powder, 8.8% Eudragit NE, 1.10% talc, 1.2% magnesium stearate. Additives disclosed for addition to the immediate release layer include disintegrating agents, diluents, binders, lubricants, antioxidants, colourings, sweeteners, and others are disclosed. Additives disclosed for addition to the prolonged release layers include those for use with the immediate release layers, excluding disintegrating agents. Guar gum, sodium alginate, and others are disclosed as disintegrating agents that comprise 0-15% of the layer. Hydroxypropylcellulose is disclosed as a binder that can comprise 0.5-25% of the layer. Hydrogenated vegetable oils are disclosed as diluents. Miconazole, benzodiazepines such as lorazepam, are disclosed as additional active agents, and the active agents are disclosed as comprising from 1-99% of the layers. The reference lacks an exemplification of a water-soluble polymer in the prolonged release granule and density. See pg. 2, line 19-pg. 12, line 38.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to exemplify the prolonged release granule of Example 1 of Saslawski et al. as further comprising hydroxypropylmethylcellulose because on page 12 of the specification Saslawski et al. teach that binders such as. . .hydroxypropylmethylcellulose. . .may be incorporated into the prolonged-release layer; thus, one of skill in the art would have been motivated to exemplify hydroxypropylmethylcellulose in the prolonged release granule of Example 1 of Saslawski et al. because of the expectation of increasing the cohesion of the granule.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to teach the tablet of Saslawski et al. as having a density of 0.1-0.5g/cc, since it has been held that discovering an optimum value of a result effective variable involves only routine skill in the art. In re Boesch, 617 F.2d 272, 205 USPQ 215 (CCPA 1980). Further, it would have been obvious to one of ordinary skill in the art at the time the invention was made to vary the density of the tablets of Saslawski et al. because of the expectation of achieving different dosage formulations of the tablet.

Claims 12 and 40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Saslawki et al. as applied to claims 1-2, 6, 7-10, 13-27, 29, 37-38, 41-43, 45-47, 49-50, 52-53, above, and further in view of Morella et al. (5,378,474).

Saslawski et al. is applied as discussed above. The reference lacks metronidazole.

Morella et al. teaches sustained release pharmaceutical compositions having a core element and a core coating. Antibiotics disclosed for use as active agents include nitrofurantoin and metronidazole. See Col. 2, line 27Col. 5, line 45; Col. 13, line 65-Col. 15, line 21.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to teach metronidazole as the active agent in Saslawski et al. because a) Morella et al. and Saslawski et al. are both directed to sustained release tablets; b) Saslawski et al. teach antibiotics such as penicillin as active agents in his compositions and Morella et al. teach penicillin and metronidazole as interchangeable antibiotics for use in controlled release tablets; thus, one of skill in the art would have been motivated to substitute metronidazole for penicillin in the tablets of Saslawski et al.

Claims 28, 33-35, 36, 44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Saslawski et al. as applied to claims 1-2, 6, 7-10, 13-27, 29, 37-38, 41-43, 45-47, 49-50, 52-53, above, and further in view of Gole et al. (5,558,880).

Saslawski et al. is applied as discussed above. The reference lacks a matrix forming agent consisting of xanthan gum, gelatin, and amino acids.

Gole et al. teaches pharmaceutical dosage forms defined by a matrix containing gelatin, pectin and one or more amino acids having form about 2 to 12 carbon atoms. Amino acids disclosed include glycine, alanine, aspartic acid, glutamic acid, hydroxyproline, isoleucine, leucine, and phenylalanine. Other matrix forming agents disclosed include gelatins and xanthan gums. It is further disclosed that polysaccharide complexes may be utilized as matrix forming agents. The matrix materials are disclosed as comprising 0.1-15% of the total solution. See Col. 2, line 40-Col. 8, line 55.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to add the matrix of Gole et al. to the immediate-release granule of Saslawski et al. because a) Gole et al. and Saslawski et al. are both directed to pharmaceuticals that provide immediate release of an active agent; b) Saslawski et al. teach many of the matrix components of Gole et al. as disintegrating agents for use in their immediate release layer; c) Gole et al. his matrices as resisting disintegration under manufacturing and handling, and as exhibiting a fast speed of dissolution upon ingestion; thus, one of skill in the art would be motivated to add the matrix of Gole et al. to the immediate release granule of Saslawski et al. because of the expectation of producing a tablet that resists disintegration under manufacturing and handling and exhibits a fast speed of dissolution upon ingestion.

Claims 10, 12, 38 and 40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hubber et al. as applied to claims 1, 2, 6-9, 13-15, 19-20, 22, 24-29, 37, 45-46, 49-50, 52-53, above, and further in view of Morella et al.

Hubber et al. is applied as discussed above. The reference lacks metronidazole.

Morella et al. teaches sustained release pharmaceutical compositions having a core element and a core coating. Antibiotics disclosed for use as active agents include nitrofurantoin and metronidazole. See Col. 2, line 27Col. 5, line 45; Col. 13, line 65-Col. 15, line 21.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute metronidazole for nitrofurantoin in Hubber et al. because a) Hubber et al. and Morella et al. are both directed to sustained release tablets; b) Hubber et al. teach antibiotics such as nitrofurantoin as active agents in his compositions and Morella et al. teach nitrofurantoin and metronidazole as interchangeable antibiotics for use in controlled release tablets; thus, one of skill in the art would have been motivated to substitute metronidazole for nitrofurantoin in the tablets of Morella et al.

Claims 1-2, 6-9, 13-15, 19-20, 22, 24-29, 37, 45-46, 49-50, 52-53 are rejected under 35 U.S.C. 103(a) as being unpatentable over Huber (4,122,157).

Huber teaches nitrofurantoin sustained release tablets. Exemplified is a tablet comprising a rapid release layer and a slow release layer, wherein the rapid release layer comprises 33% nitrofurantoin and 67% inert pharmaceutical excipients, and the slow release layer comprises 36% nitrofurantoin, 31% hydroxypropylmethylcellulose, and 33% inert pharmaceutical excipients. Diluents, binders, lubricants, disintegrating agents, coloring agents, and flavoring agents are disclosed as pharmaceutical excipients. Binders (matrix forming agents) disclosed for

use in the fast release layer are starch, gelatin, sucrose, dextrose, molasses, acacia, sodium alginate, carboxymethylcellulose and polyvinylpyrrolidone. Hydrogenated vegetable oil is disclosed as a lubricant. In the claims, hydroxypropyl methylcellulose is disclosed as comprising 14-42% of the tablet. Thus, Huber and the instant invention both teach composition comprising a sustained release layer and a fast release layer, wherein the slow release layer comprises 31% of a water-soluble polymer (hydroxypropylmethylcellulose), hydrogenated vegetable oil and 36% of an active agent (nitrofurantoin), and the fast release layer comprises matrix forming agents (binders, such as gelatin and starch), and 33% of an active agent (nitrofurantoin). See Col. 1, line 6-Col. 7, line 35. The reference lacks teachings of density.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to teach the tablet of Hubber et al. as having a density of 0.1-0.5g/cc, since it has been held that discovering an optimum value of a result effective variable involves only routine skill in the art. In re Boesch, 617 F.2d 272, 205 USPQ 215 (CCPA 1980). Further, it would have been obvious to one of ordinary skill in the art at the time the invention was made to vary the density of the tablets of Hubber et al. because of the expectation of achieving different dosage formulations of the tablet.

Claims 33-35, 36, 41-44, are rejected under 35 U.S.C. 103(a) as being unpatentable over Hubber et al. as applied to claims 1, 2, 6-9, 13-15, 19-20, 22, 24-29, 37, 45-46, 49-50, 52-53, above, and further in view of Gole et al.

Hubber et al. is applied as discussed above. The reference lacks matrix agents consisting of gelatin, xanthan gum, and amino acids.

Gole et al. is applied as discussed above.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to add the matrix of Gole et al. to the fast release portion of Hubber et al. because a) Gole et al. and Hubber et al. are both directed to pharmaceuticals that provide immediate release of an active agent; b) Hubber et al. teach many of the matrix components of Gole et al. as disintegrating agents for use in their fast release portion; c) Gole et al. his matrices as resisting disintegration under manufacturing and handling, and as exhibiting a fast speed of dissolution upon ingestion; thus, one of skill in the art would be motivated to add the matrix of Gole et al. to the fast release portion of Hubber et al because of the expectation of producing a tablet that resists disintegration under manufacturing and handling and exhibits a fast speed of dissolution upon ingestion.

Claims 16-18, 21, 23, 47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hubber et al. as applied to claims 1, 2, 6-9, 13-15, 19-20, 22, 24-29, 37, 45-46, 49-50, 52-53, above, and further in view of Saslawki et al.

Hubber et al. is applied as discussed above. The reference lacks preferred percent weights of fatty acids and active ingredients.

Saslawski et al. is applied as discussed above.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate the percent weights of fatty acids and active agents taught by Saslawki et al. into the invention of Hubber et al. because a) both Saslawski et al. and Hubber et al. teach sustained release tablets comprising a sustained release layer comprising a water-soluble polymer and an active agent and a fast release layer comprising a matrix forming agent and an active agent; and b) it has been held that where the general conditions of a claim are disclosed in

the prior art, discovering the optimum or workable ranges involves only routine skill in the art. In re Aller, 105 USPQ 233.

Response to Arguments

Applicant argues, "Huber relates to a compressed tablet suitable for oral administration having two discrete portions. . .the structure of a compressed tablet and a freeze-dried composition are quite different". This argument is not persuasive. The Examiner respectfully points out instant claim 1 is a product-by-process claim. Even though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process. In re Thorpe, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985). See MPEP 2113. Furthermore, the Examiner respectfully points out that Applicant has provided no evidence that the tablets of the instant invention are distinct from those of the prior art, though the tablets of the prior art and the instant invention are comprised of the same constituents.

Applicant argues, "As with the other compressed tablet structures, that of Saslawski does not have the channeled structure of a lyophilized product, nor could it be freeze-dried as it has no water present in the structure". This argument is not persuasive. Again, the Examiner respectfully points out that even though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. Furthermore, Applicant has provided no evidence that the tablets are distinct from each other, though they comprise the

same constituents. The Examiner respectfully points out that showings of fact are much preferred to statements of opinion. In re Oelrich, 198 USPQ 210, 215 (CCPA 1978).

Applicant argues, "Saslawski et al. contemplates a 'prolonged release layer' containing 'inert' materials rather than water soluble polymers as in the compositions of applicants' invention". This argument is not persuasive. The Examiner respectfully points out that while Saslawski et al. does not exemplify such a composition, Saslawski teaches that binders such as hydroxypropylmethylcellulose may be incorporated into the prolonged-release layer. For motivation to exemplify such a formulation, see the above rejection.

Applicant argues, "Morella et al. . .relates to an oral tablet. . .but nowhere does it indicate that the outer coating should be utilized for fast release of drug". This argument is not persuasive, as Morella et al. is merely relied upon to teach metronidazole as a pharmaceutical active agent.

Applicant argues, "Nowhere do any of the cited patents describe or suggest the combination of compressed tablets and lyophilized materials". This argument is not persuasive. Again, the Examiner respectfully points out that the process steps are not given patentable weight in the instant claims.

Applicant argues, "the applicability of the In re Aller case is limited in this situation because the freeze-dried compositions of applicants' invention are not simply 'optimized' versions of the Huber et al. and/or Saslawski et al. patents. Rather, they are different in form and function in that their structures preserve the volume of the product". This argument is not persuasive. The Examiner respectfully points out that In re Aller is relied upon in a secondary

fashion to show that it is routine in the art to vary ranges, such as percent weights of fatty acids and active ingredients.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lauren Q Wells whose telephone number is (703) 305-1878. The examiner can normally be reached on M-F (7-5:30), with alternate Mondays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on (703)305-1877. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1234.

lqw
May 29, 2003

SREENI PADMANABHAN
PRIMARY EXAMINER

6/1/03